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EDITORIAL COMMENT

Cardiac Positron Emission Tomography/Computed Tomography Imaging of the Renin-Angiotensin System in Humans Holds Promise for Image-Guided Approach to Heart Failure Therapy*

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Coronary artery disease (CAD) is the prevalent underlying mechanism for the majority of patients with heart failure, followed by idiopathic cardiomyopathy, valvular disease, and hypertensive heart disease (1). Despite major advancements in the treatment of heart failure with beta-blockers, angiotensin-converting enzyme (ACE) inhibition, angiotensin II type 1 receptor (AT-1) blockers, and aldosterone that impact morbidity and mortality, 5-year mortality rates for heart failure still remain as high as 50%. In the United States, more than 4 million people suffer from heart failure (2), and in view of an increasingly elderly population, the prevalence of this disease is likely to continuously increase.

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Left ventricular (LV) remodeling, defined clinically as alterations in volume, shape, and/or function of the heart chambers in response to chronically elevated loading conditions, has been appreciated as a central determinant of the clinical course and outcome of systolic heart failure. Apart from the catecholamine actions and the development of interstitial myocardial fibrosis, the myocardial renin-angiotensin system (RAS) has been closely related to the central maladaptive cellular and molecular alterations that parallel LV remodeling. LV remodeling is characterized by limited hypertrophic growth, remodeling of cardiac myocytes with reactivation of fetal gene program, progressive loss of contractile proteins, defective excitation-contracting coupling, interstitial fibrosis, and a decreased responsiveness to beta-adrenergic stimulation (3). Despite such adaptive myocardial alterations to produce more efficient oxygen consumption, better energy generation, and prolonged cell survival, there is a continuous cell loss during the cardiac remodeling process via necrotic, apoptotic, and most likely, autophagic pathways (3). Not surprisingly, numerous large randomized clinical trials have demonstrated direct beneficial effects of RAS blockade on clinical symptoms and outcomes of patients with LV systolic dysfunction (2). ACE inhibitors, AT-1 blockers, and aldosterone antagonists have been successfully applied to prevent or at least delay LV remodeling associated with a marked improvement in clinical symptoms, reduction in hospitalization, and mortality rates in patients with systolic dysfunction. Conversely, it has also been recognized that a marked interindividual variability in response to RAS blockade may exist, ranging from distinct clinical benefit to no detectable benefit and even to serious adverse reactions (4). The underlying mechanisms for the described variety in individual responses to medical heart failure therapy remains uncertain, but they have been related to differences in race, ethnicity, comorbid conditions, concomitant use of other medications, and certain genetic predispositions (3,5). Another potential mechanism for the large variability in individual responses to the inhibition of the RAS may be seen in the myocardial tissue component of the RAS, which is largely independent of its systemic component and not accessible to routine laboratory testing (6). In view of the described variability in myocardial response to medical RAS blockade, the identification and characterization of the myocardial tissue component or the RAS system with molecular imaging in the individual heart failure patient is highly desirable (Table 1). It is anticipated that such a diagnostic approach would provide more precise information to predict and monitor the myocardial response to medical RAS blockade.

Targeting cardiac angiotensin II type I receptors. In this issue of the *Journal*, Fukushima et al. (7) describe a novel AT-1 receptor ligand [^{11}C]-KR31173 combined with PET/CT that targets the angiotensin II subtype 1 receptor (AT1R) of the human heart. As it was observed in 4 healthy volunteers, myocardial retention of [^{11}C]-KR31173 was visually detectable, homogenously distributed in the myocardium, and stable over time. However, it is important to note that myocardial retention of KR31173 in these healthy human subjects was significantly lower than those in normal healthy pigs (1.2 ± 0.1%/min vs. 4.4 ± 1.2%/min). Moreover, after pre-treatment with olmesartan, only 54% of the receptors (1.3 ± 0.1%/min to 0.7 ± 0.1%/min) were blocked, suggesting limited specificity. Nonetheless, this

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Table 1 Molecular Radiotracers That Target the Renin-Angiotensin System

Angiotensin-Converting Enzyme	Angiotensin II Type 1 Receptor
^{18}F-fluorocaptopril	^{11}C-MK-996
^{11}C-zofenoprilat	^{11}C-L-159884
^{125}I-iodotyrosyl-lisinopril	^{11}C-KR31173
^{18}F-fluorobenzoyl-lisinopril	^{99m}Tc-losartan
^{99m}Tc-(CO)3D(C_8)-lisinopril	

first-in-man application of receptor ligand [^{11}C]-KR31173 combined with PET/CT confirmed the presence of local tissue RAS in human hearts, proved to be safe, and showed that the signal was high enough to allow external imaging with PET. Additional experiments performed in young farm pigs under healthy conditions and 3 to 4 weeks after myocardial infarction showed AT1R up-regulation in the infarcted area when compared with remote myocardium. Further, the retention of KR31173 in infarcted and remote myocardium (8.7 ± 0.8%/min and 7.1 ± 0.3%/min) was significantly higher than in the myocardium of healthy pigs (5.8 ± 0.4%/min). In postmortem immunohistochemistry analysis, anti-AT1R antibody binding was localized to spindle-shaped cells, presumably myofibroblasts, in the infarct region, whereas there was also significant binding to cardiomyocytes in remote areas. These findings in pigs are similar to those observed in an experimental mouse model of post-infarction heart failure in which in vivo AT1R imaging was accomplished with ^{99m}Tc losartan micro–single-photon emission CT/CT and immunohistochemical analysis showed binding of the radiotracer almost exclusively in the myofibroblast rather than cardiomyocytes (8). Thus, although the [^{11}C]-KR31173 imaging signal identifies AT1R expression in the myocardium, it does not differentiate between myofibroblast and cardiomyocyte cell types, and with 54% of the receptors blocked after pre-treatment with an AT-1 blocker, it has limited specificity. In this direction, the combination with other molecular imaging probes, such as radiolabeled ACE inhibitors to investigate the LV remodeling process could prove to be useful in heart failure patients (Fig. 1).

Targeting cardiac ACE. An alternative molecular imaging strategy is to image and monitor myocardial ACE-1 up-regulation as a function of progressive heart failure. ACE-1 is a large type I anchored glycoprotein that is located extracellularly along the surface of the myocardial cell membrane. ACE inhibitors bind to these extracellular enzyme binding sites and in large clinical trials have shown to improve patient mortality, prevent or reverse LV remodeling, and improve quality of life (9–11). External cardiac imaging using radiolabeled ACE inhibitors may give a direct measure of tissue ACE expression in the myocardium. High-affinity ^{18}F-fluorobenzoyl-lisinopril has been shown to specifically localize in ex vivo myocardial samples obtained from explanted cardiomyopathic hearts in cardiac allograft recipients by autoradiography (12,13). In human ACE-1 overexpressing transgenic rats, technetium-99m–labeled lisinopril was shown to provide a signal intensity that is sufficiently high to allow external micro–single-photon emis-

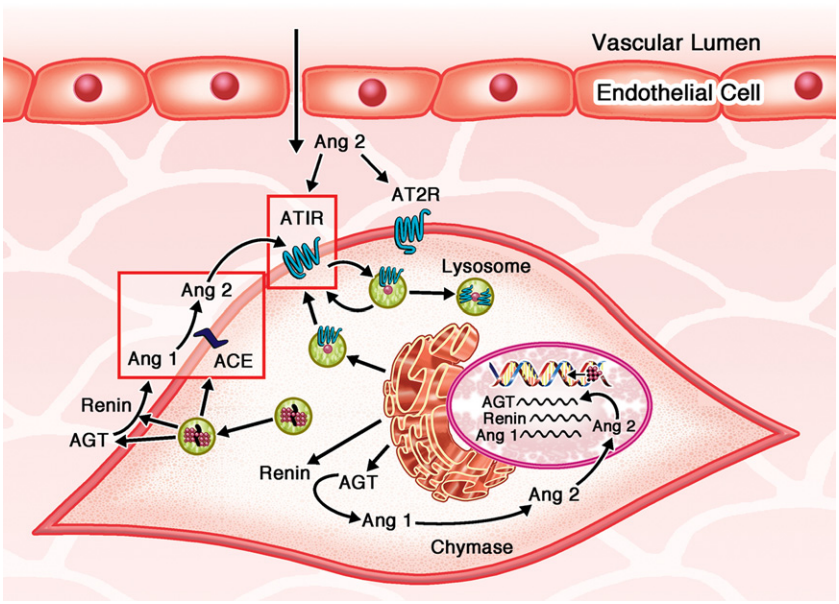

Figure 1 Diagrammatic Representation of Myocardial Cell and Potential Targets of Radiotracer Imaging and Mapping of the Surface RAS

ACE = angiotensin-converting enzyme; AGT = angiotensinogen; Ang II = angiotensin II; AT1R = angiotensin II type 1 receptor; AT2R = angiotensin II type 2 receptor; mRNA = messenger RNA; RAS = renin-angiotensin system.

sion CT/CT imaging (14,15). Given that the initiation of the RAS process starts early in the failing heart with activation of the ACE-1 activity within the cardiomyocytes (16,17) rather than the downstream effects of angiotensin II on AT1R, targeting the imaging to ACE itself could be more sensitive (Fig. 1). Moreover, ACE to Ang II production is independent of AT1R regulation, which could make ACE imaging more specific.

Imaging patients with heart failure. As the authors acknowledge, the feasibility and diagnostic value of RAS imaging in heart failure patients due to myocardial infarction or other pathological conditions remain to be tested. Although high-affinity radiotracers provide high target-to-nontarget ratios in vivo with specific binding to a target protein, in disease states such as heart failure, it is perhaps more important to develop a probe at high specific activity that is sensitive to changes in target protein as a function of disease or treatment. Accordingly, it is ultimately the Bmax (total available target protein), $Bmax/K_D$ (ratio of target density to equilibrium dissociation constant), and receptor occupancy of these radiotracers that will determine the best-suited potential probe for in vivo imaging of heart failure patients. Maximum in vivo binding potential of a radiotracer can also be influenced by other factors, such as nonspecific binding, free fraction either in plasma or in the target milieu, the exclusion of metabolites, and specific binding to other targets (17). Beyond the radiopharmaceutical design and characterization, the regulation of AT1R and recycling and/or degradation of AT-1 receptor are key to imaging. Receptor expression can be altered from normal to diseased state, and can be affected by a multitude of factors, and in any one of the steps of transcription, translation, or trafficking.

ACE-1 imaging with high-affinity ^{99m}Tc–labeled lisinopril, as another myocardial tissue RAS imaging probe, may provide invaluable information in identifying other molecular mechanisms leading to the initiation and progression of systolic heart failure upstream of the myocardial AT-1 receptors (14). Such a hybrid molecular imaging approach could contribute to a better understanding of the effects of ACE inhibition alone or in combination with AT-1 blockers on LV hypertrophy in hypertensive patients (18) and may further elucidate the link between renal and cardiovascular disease (19). In addition, for a comprehensive evaluation of the RAS in heart failure patients, research activities should also be directed to image the expression of angiotensin II type 2 receptors in the myocardium. The development of such molecular imaging probes to potentially personalize and guide the medical treatment of heart failure patients appears of utmost importance because the promise has not yet been mitigated by a decade of investigation with biomarkers, such as pro-brain natriuretic peptide or cardiac troponin T, and genomics (2).

Conclusions. The work published by Fukushima et al. (7) represents an important translational step of previous experimental investigations for identification and characterization of AT1R expression in the normal human heart, whose application in heart failure patients, however, remains untested. Such image-guided molecular approach holds promise to ultimately enable earlier and more precise identification and characterization of heart failure, and the assessment and monitoring of the therapeutic responses in individual patients. Whether such image-guided and personalized medical intervention aiming to prevent or delay the progression of LV remodeling will ultimately result in improved patient outcome requires clinical verification.

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